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New therapeutic approaches to target gut-brain axis dysfunction during anorexia nervosa

Najate Achamrah [a, b, c, *], Pierre Déchelotte [a, b, c], Moïse Coëffier [a, b, c]

[a] Nutrition Department, Rouen University Hospital Center, Rouen, France
[b] Normandie Univ, URN, INSERM UMR 1073, Nutrition, Inflammation et dysfonction de l'axe Intestin-Cerveau, IRIB, Rouen, France
[c] Clinical Investigation Centre CIC 1404, INSERM and Rouen University Hospital, Rouen, France

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Dysregulation of gut-brain axis seems to play a key role in anorexia nervosa (AN) pathophysiology. Central alterations of hypothalamic–pituitary–adrenal axis, neurotransmission, food intake regulation, and peripheral alterations of gut barrier, gut microbiota, immune system, have been reported in AN. Potential beneficial effects of physical activity on gut-brain axis have been observed during refeeding in AN. As nutritional support, psychotherapy, anxiolytics, antidepressants, programmed physical activity needs to be considered as a novel therapeutic tool in AN management. In the future, combined strategies of gut-brain modulations should be assessed in AN, including other promising candidates, probiotics, glutamine and omega-3 fatty acids.

Abbreviations: 5-HT, serotonin; ABA, activity-based anorexia; ACTH, adrenocorticotropin hormone; AN, anorexia nervosa; CRH, corticotrophin-releasing hormone; HPA, hypothalamic-pituitary-adrenal; IDO, indolamine-2,3-dioxygénase; KAT, kynurenine aminotransferase; KYN, kynurenine; KYNA, kynurenic acid; QA, quinolinic acid; SCFAs, short-chain fatty acids; TDO, tryptophane dioxygénase; TLR, Toll Like Receptor; TRP, tryptophan; α-MSH, α-melanocyte-stimulating-hormone.

* Corresponding author. Najate Achamrah, Department of Clinical Nutrition, Rouen University Hospital, 1 Rue de Germont, 76000 Rouen, France.
E-mail address: najate.achamrah@chu-rouen.fr (N. Achamrah).

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1. Introduction

Anorexia Nervosa (AN) is an eating disorder characterized by malnutrition (body mass index less than 18.5 kg/m^2), an obsessive fear to gain weight and a disturbed self-body image [1]. Although recovery is expected in one half of AN patients after 10 years, chronic symptoms and somatic complications will occur in the other half. Psychiatric disorders complications such as anxiety or depression are frequent [2]. Fortunately, the mortality after 10 years has declined from earlier reports of over 10% [3], to 1–5% in more recent series [4], which still highlights the severity of the disease. The lack of prevention, late diagnosis and insufficient therapeutic tools lead to high AN morbi-mortality. Moreover, a better understanding of its complex and multifactorial pathophysiology is needed. Activity-based anorexia (ABA) is a well established animal model mimicking alterations observed in AN, self-food restriction associated with increased physical activity, and altered behaviour [5]. Dysregulation of gut-brain axis involving central alterations of hypothalamic-pituitary-adrenal (HPA) axis, neurotransmission, food intake regulation, and peripheral alterations of gut barrier, gut microbiota, immune system, seems to play a key role in AN pathophysiology [6] (Fig. 1). Conventional therapeutic strategies integrate nutritional and psychological supports, while programmed physical activity arouses growing interest [7]. Indeed, programmed physical activity may reduce psychiatric symptoms, i.e. depression, anxiety [8], and improve body composition restoration through an increase of lean mass, and a better body distribution of fat mass [7].

After reporting the central and peripheral alterations observed during AN, we review here the potential effects of physical activity on gut-brain axis during refeeding, and propose future combined strategies for AN treatment.

2. Dysregulation of gut-brain axis in anorexia nervosa

2.1. Central alterations

2.1.1. HPA axis activation

Activation of the HPA axis through high plasmatic levels of cortisol and corticotrophin-releasing factor (CRF) have been observed in AN patients [9], and decreased after treatment [10]. Recently, Scharner et al. reported activation of CRF in distinct brain nuclei, in female ABA mice [11]. Intracerebroventricular administration of a CRF antagonist attenuated the development of ABA, in a previous study [12]. Thus, the increase of CRF signalling seems to play a pathogenetic role in the development and/or maintenance of AN [13].

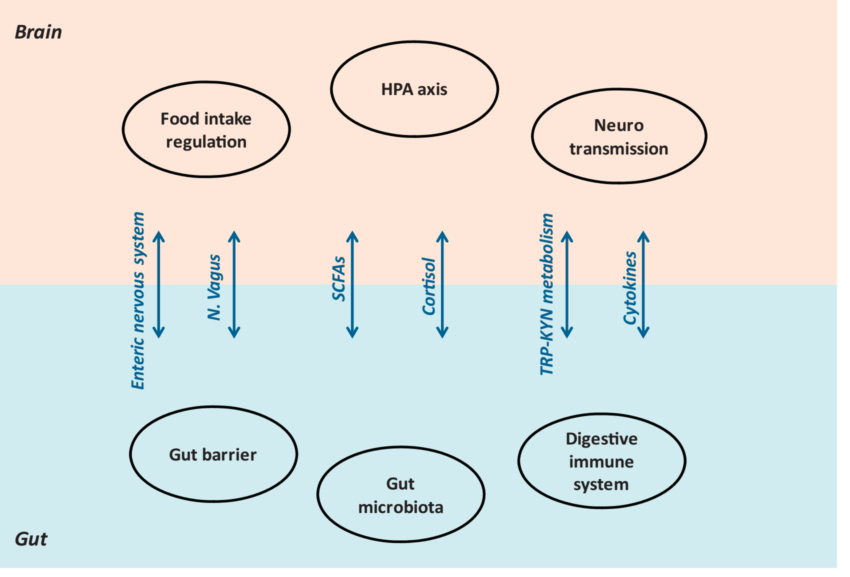

Fig. 1. Dysregulation of gut-brain axis in anorexia nervosa. Pathophysiology of anorexia nervosa involves central alterations of hypothalamic-pituitary-adrenal (HPA) axis, neurotransmission, food intake regulation, and peripheral alterations of gut barrier, gut microbiota and immune system. Many actors can modulate gut-brain axis including nervous (vagus, enteric nervous system), immune (cytokines), endocrine (cortisol), short-chain fatty acids (SCFAs), tryptophan-kynurenine metabolites (TRP-KYN).

2.1.2. *Tryptophan metabolism*

Dysfunction of central monoaminergic systems has also been reported in AN. Low plasmatic concentrations of serotonin and its precursor, tryptophan (TRP), have been observed in AN patients [14]. Serotonin plays a major role in the regulation of behaviour, emotions and also in gastrointestinal motility [15]. In central and peripheral (liver, muscle, intestine) tissues, TRP is also metabolized by Indolamine-2,3-dioxygénase (IDO) and Tryptophane dioxygenase (TDO) enzymes into kynurenine (KYN) which is the precursor of both neuroprotective kynurenic acid (KYNA) and neurotoxic quinolinic acid (QA) by Kynurenine aminotransferase (KATs) and Kynurenine-3-monooxygenase (KMO) enzymes, respectively [16]. TRP-KYN metabolism arouses growing interest in the study of neuropsychiatric disorders, anxiety and depression [15]. Low KYNA/KYN plasma ratios are associated with depression and anxiety. Moreover, dysfunction of TRP-KYN metabolism has been also involved in AN pathophysiology [14,17]. Interestingly, activation of HPA axis, increased plasmatic cortisol and inflammation are known to activate TRP-KYN metabolism, leading to little available TRP for serotonin synthesis, resulting in psychiatric (anxiety, depression) and gastrointestinal disorders (Fig. 2). During refeeding in AN patients, Gauthier et al. reported that anxiety/depression symptoms were correlated both to the ratio TRP/total amino acids and the plasmatic serotonin levels [14].

2.1.3. *Central food intake regulation*

Stress plays an important role in the AN pathophysiology. It has been reported to be involved in dysfunction of central food intake regulation through the production of auto-antibodies directed against neuropeptides, such as the anorexigenic α-melanocyte-stimulating-hormone (α-MSH) [18–20]. Recently, structural homologies have been reported between α-MSH and an intestinal bacterial protein secreted by *Escherichia coli*, ClpB [21], which activates satiety pathway in rats [22]. These findings suggest a role of gut microbiota composition in AN pathophysiology.

2.1.4. *Reward system*

Neurobiological evidences suggest that alterations of the reward system are involved in the pathophysiology of AN [23]. Structural and functional dysfunctions of brain regions involved in the reward

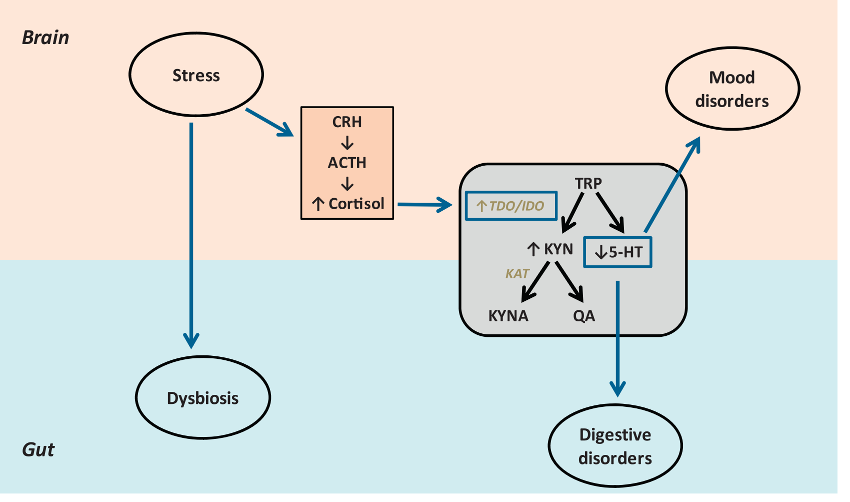

Fig. 2. The role of stress in anorexia nervosa pathophysiology. Activation of HPA axis, increased plasmatic cortisol and inflammation are known to activate TRP-KYN metabolism, leading to little available TRP for serotonin synthesis, resulting in mood (anxiety, depression) and gastrointestinal disorders. HPA: hypothalamic-pituitary-adrenal, CRH: corticotrophin-releasing hormone, ACTH: adrenocorticotropin hormone, TRP: tryptophan, KYN: kynurenine, 5-HT: serotonin, KYNA: kynurenic acid, QA: quinolinic acid, TDO: tryptophane dioxygénase, IDO: indolamine-2,3-dioxygénase, KAT: kynurenine aminotransferase.

system, i.e. from the ventral tegmental area to the nucleus accumbens, have been reported both in ABA model [24] and also in AN patients [6]. Alteration of dopamine neuronal activity may explain the lack of pleasure during feeding in AN patients. Moreover, it has been hypothesized that AN patients exhibit an addiction to starvation [25]. Gut-brain axis seems to play a pathophysiological role in the dysfunction of the reward system in AN. Indeed, to increase food intake and counteract undernutrition, orexigenic neuropeptides are up-regulated in AN through an adaptive mechanism. Ghrelin, an orexigenic peptide mostly synthetized by the endocrine cells of the stomach, exerts both peripheral and central effects including the modulation of the dopaminergic reward system. Ghrelino-resistance has been documented in AN patients [26]. Data from animal studies suggest that the reward system is targeted by peripheral ghrelin to influence emotional process associated with food [27]. In AN patients, an altered impact of ghrelin on the reward system might result in food aversion. However, clinical data are still lacking to confirm this hypothesis.

2.2. *Peripheral alterations*

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xposure to psychological, environmental and/or physical stressors either during childhood [28] or in adults may contribute to HPA axis alterations. These stressors are known to induce changes in gut microbiota composition and function resulting in a dysbiosis that compromises gastrointestinal function, and facilitates passage of gut microbes and their metabolites into circulation leading to inflammation [29].

2.2.1. *Gut microbiota*

Gut microbiota has been reported to play a role in many metabolic functions, i.e. regulation of body weight, energy yield from diet, intestinal immune system maturation, insulin secretion [30]. Gut microbiota also contributes to TRP-KYN metabolism either by producing metabolites, i.e. Indole-3-aldehyde [31], or by regulating KYN production in intestinal cells [32]. Alterations of gut microbiota have been associated with depression and anxiety which are frequent in AN patients [33]. Several studies reported modifications of gut microbiota in AN patients [34,35], as well as in ABA mice [36].

Moreover, AN patients with dysbiosis exhibited greater anxiety and depression symptoms [37], altered short chain fatty acid (SCFA) profiles and gastrointestinal symptoms [38]. Refeeding does ameliorate neither feacal microbiota and SCFA profiles, nor gastrointestinal symptoms [38].

Futhermore, an increase of mucin degrading bacteria (*Prevotella*) has been reported in ABA mice, which could lead to alteration in intestinal permeability [36].

2.2.2. Intestinal barrier

Alteration of intestinal barrier has been reported in ABA mice through an increase of colic permeability associated with a decreased expression of the tight junction protein claudin-1 [5]. To our knowledge, only one clinical study has evaluated intestinal permeability during AN and reported a surprising decrease of it [39]. However, some methodological aspects limited this study: patient's body mass index was not severely low (16.7 kg/m^2 on average), disease duration was unknown and the lactulose-mannitol test used explored only the small intestine permeability. Further clinical studies are needed to evaluate intestinal permeability in AN.

2.2.3. Inflammation

In AN patients, intestinal barrier alterations combined with dysbiosis may lead to bacterial translocations resulting in systemic inflammation. In a recent meta-analysis, AN was associated with a plasmatic increase of proinflammatory cytokines IL-1 β, IL-6 and TNF-α [40], which have been reported to have anorexigenic effects [41–43]. We recently observed an activation of Toll Like Receptor 4 (TLR4) signalling pathway in colonic epithelial cells and macrophages of female ABA mice, leading to downstream mucosal cytokine production [44]. Moreover, IL-1β and IL-1R1 were also increased in hypothalamus, and plasmatic corticosterone also increased. Interestingly, TLR4-*Knockout* mice exhibited greater vulnerability to ABA model with increased mortality rate suggesting a key role of TLR4, and more widely of immune system, in the pathophysiology of AN.

Nowadays, AN patients management is based on nutritional support, psychotherapy, drug administration to reduce anxiety and/or depression, but a treatment that targets the causal factors of AN is still lacking. Programmed physical activity needs to be considered as a novel therapeutic tool in AN management.

3. Potential effects of physical activity during refeeding on gut-brain axis

As reported by a recent meta-analysis, physical activity has protective effects against depression [45]. In AN patients, few clinical studies assessed the effects of programmed physical activity during refeeding on psychological status. In 21 AN patients, Szabo et al. reported that 8 weeks of resistance training resulted in a significant decrease in the Beck Depression Inventory score, a widely used psychometric test for measuring depression severity, from 21.9 ± 17.4 to 10.1 ± 9.9 [46]. Calogero et al. observed a reduction in exercise compulsivity and dependence in 63 AN patients who weekly underwent programmed physical activity [47].

Recently, we reported that maintaining physical activity through free-access to a running wheel during refeeding in male ABA mice was associated with less alterations of behaviour in dark–light boxes test, compared to ABA mice refed without physical activity. In addition, plasma corticosterone level was significantly higher in ABA-NPA mice, attesting of an activation of HPA axis, and suggesting an anxiolytic effect of physical activity during refeeding [48].

The underlying mechanisms have been poorly studied. Modifications of TRP-KYN metabolism have been proposed to explain beneficial effects of physical activity on behaviour and mood [49]. Accordingly, we reported that mice reefed without physical activity exhibited lower muscle levels of mRNA encoding for KAT enzymes than mice reefed with physical activity. In addition, higher level of plasma KYNA was observed in mice reefed with physical activity compared to the others [48], suggesting that physical activity during refeeding may increase conversion of KYN into KYNA which do not cross blood–brain barrier. We hypothesize that these central modifications could lead to higher disponibility of TRP for serotonin synthesis leading to better psychological status. Whether central modifications of TRP-KYN metabolism could explain beneficial effects of physical activity during refeeding in AN needs further investigations.

Few clinical studies reported beneficial impact of physical activity on gut microbiota diversity. In adult women with active lifestyles, increased fecal *Akkermensia muciniphila* has been observed compared with sedentary age-matched women [50]. *A. muciniphila* has been inversely associated with obesity, diabetes, cardiometabolic diseases and low-grade inflammation [51]. Likewise, significantly higher gut microbiota diversity with increased representation of 22 distinct taxa, including *A. muciniphila*, has been reported in rugby athletes compared to sedentary groups matched for age, gender and body size [52]. Additionally, higher representation of SCFA-producing bacteria has been observed in athletes compared to sedentary subjects [53,54].

Moreover, in *ad libitum* male rats with free access to an activity wheel, Queipo-Ortuno et al. observed a significant increase of *Blautia coccoides Eubacterium rectale* bacteria group [36]. Interestingly, this specific group involves most of the butyrate-producing bacteria in human gut [55]. Butyrate is a SCFA that has beneficial effects on intestinal barrier integrity by increasing tight junctions' assembly [56], mucin synthesis [57], leading to decreased bacteria translocations [58]. Likewise, in a mice model of chronic stress-induced intestinal barrier dysfunction, moderate exercise maintained intestinal permeability, attenuated bacterial translocations, and increased gene expression and protein levels of four antimicrobial peptides (alpha-defensin 5, beta-defensin 1, Reg IIIbeta and Reg IIIgamma) [59]. In mice, exercise may also modulate intestinal immune response by decreasing TNF-α, proinflammatory cytokines (IL-17), and increasing antioxidant enzymes (e.g. glutathione peroxidase), antiinflammatory cytokines (IL-10), and antiapoptotic proteins (Bcl-2) in intestinal lymphocytes [60–62].

To our knowledge, no clinical study assessed the effects of programmed physical activity during refeeding neither on gut microbiota diversity nor intestinal permeability in AN patients. In undernourished ABA mice, enhanced colonic permeability has been reported [5]. After refeeding, colonic permeability was significantly enhanced in ABA-NPA, compared to ABA-PA [48], suggesting a beneficial effect of physical activity on intestinal barrier integrity.

4. Perspectives: toward new combined strategies?

Programmed physical activity during refeeding in AN patients seems to result in a beneficial impact on gut-brain axis. But, the synergistic role of nutrients, i.e. whether an unhealthy diet can antagonize the benefices of physical activity, needs further investigations. Clarke et al. reported previously that the gut microbiota diversity of rugby athletes was correlated with their dietary protein intake [52].

Moreover, in the future, programmed physical activity should probably be combined with other new strategies of gut-brain modulations. Probiotics are promising candidates. *A. muciniphila* alive or pasteurized has been reported in mice to restore gut barrier function by interacting with TLR2, restoring tight junction proteins expression, and increasing mucus later thickness [51]. However, human studies are still needed. Recently, Marin et al. reported that restoring intestinal *Lactobacillus* levels improved the behavioral abnormalities in chronically stressed mice displaying despair behaviour [32]. Interestingly, *Lactobacillus* administration was associated with the inhibition of the enzyme IDO1 expression. Given IDO1 is responsible of the conversion of TRP into KYN in the intestine, its inhibition leads to decreased circulating level of KYN. These results suggest the mechanistic role of TRP-KYN metabolism during nutritional modulations of gut-brain axis.

Likewise, omega-3 fatty acids may also be an interesting candidate for gut-brain axis modulation in AN. Beneficial effects of omega-3 fatty acids have been reported on intestinal barrier integrity by decreasing inflammation and intestinal permeability in an animal model of colitis [63]. In addition, omega-3 fatty acids supplementations have been associated with improvement of depression scores in randomized clinical studies [64–66]. Few conflicting studies assessed the effects of omega-3 fatty acids supplementation in AN patients. Ayton et al. reported an improvement of anxiety level in 7 AN patients after 3 months of supplementation with Eicosapentaenoic acid (EPA) (1 g/day) [67]. Inversely, Barbarich et al. observed that 6 months supplementation with combined Docosahexaenoic acid (DHA) (600 mg/day), TRP (2,3 g/day), arachidonic acid (180 mg/day), and omega-6 fatty acids, in 26 AN patients did not increase Fluoxetine effects [68]. To our knowledge, no study assessed effects of omega-3 fatty acids on intestinal barrier in AN. Further investigations are still needed to recommend the prescription of this specific nutrient during refeeding in AN.

Finally, among specific nutrients that could modulate gut-brain axis, glutamine is also an interesting candidate [69]. This amino acid plays a key role in intestinal barrier integrity by stimulating *in vitro* proliferation of enterocytes, *in vitro* and *in vivo* intestinal protein synthesis, *in vitro* restoration of tight junction protein expression and localisation. Moreover, glutamine supplementation prevented intestinal hyperpermeability in mice model of irritable bowel syndrome. Further research is needed to identify the central effects of glutamine in AN. Interestingly, Kawase et al. focused recently on the relationship between the gut microbiota and the brain amino acids in specific pathogen-free (SPF) and germ-free (GF) mice [70]. L-glutamine concentrations were higher in SPF than in GF mice both in plasma and brain. Given glutamine's brain concentration seems to be dependent on the presence of gut microbiota, nutritional modulations could probably modify central glutamine metabolism. Further investigations are needed to better understand the effects of this amino acid on gut-brain axis and to propose it as a new therapeutic tool in AN.

5. Conclusion

AN pathophysiology is complex and multifactorial involving gut-brain axis alterations. As the disease and undernutrition are entangled, discerning the cause and the consequences is challenging in clinical practice. Animal studies are thus useful to better understand these mechanisms. During refeeding, potential beneficial effects of programmed physical activity have been reported. Further large clinical studies are needed to confirm that programmed physical activity should be considered as a therapeutic tool in AN. Effect of combined strategies of gut-brain modulations should also be assessed in AN, including promising candidates, probiotics, glutamine and omega-3 fatty acids.

Conflicts of interest

Authors have no conflict of interest to declare.

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